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Scientific evidence on the usefulness of intraarticular hyaluronic acid injection in the management of temporomandibular dysfunction

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Abstract

Hyaluronic acid (HA) is found in high concentrations in cartilage and synovial fluid, and is an important component of the extracellular matrixes – exerting joint lubrication and buffering actions thanks to its viscoelastic properties. The present study examines the scientific evidence found in the current literature on the usefulness of the intraarticular injection of HA in patients with temporomandibular dysfunction.

A literature search was made up until May 2008 in the following databases: PubMed / MEDLINE. Of the articles found in the literature, the present review included 18 relevant studies on the application of HA in the temporomandibular joint (TMJ). The quality, level of evidence and strength of recommendation of the articles was evaluated based on the “Strength of Recommendation Taxonomy” criteria.

It is concluded that type A level of recommendation exists in favor of the intraarticular injection of HA in dysfunction of the TMJ. However, further studies are needed to establish the true therapeutic effects and to identify the best dosing regimen.

Key words: Hyaluronic acid, temporomandibular dysfunction, temporomandibular joint.

Introduction

Hyaluronic acid (HA) is a linear, hydrophilic, polyanionic high molecular weight polysaccharide exclusively composed of repeated disaccharide units of glucuronic acid and N-acetylglucosamine. HA is a natural component of joint synovial fluid, and is also found in the extracellular matrix of connective tissue (1,2). The authors

that make use of HA consider that the intraarticular injection of HA in patients with temporomandibular joint dysfunction (TMJD) improves function and lessens pain. The excellent mechanical and metabolic properties of the molecule define it as an ideal treatment for inflammatory problems of the temporomandibular joint (TMJ) (3,4).

The mechanical action of HA is based on joint lubrication and consequently lessened joint wear secondary to adhesions, with a reduction in friction within the intraarticular space. HA also reduces the levels of inflammatory mediators, thus contributing to afford relief from joint pain (1,2, 4-7). Its metabolic activity in turn involves the facilitation of nutrition in avascular zones of the joint disc and cartilage. HA acts in the combination of glycosaminoglycans to form proteoglycan, which under pathological conditions disintegrates and disperses within the synovial cavity (4-8). Despite the fact that its half-life is about 13 hours, the intraarticular application of HA offers persistent beneficial effects (2,3,7).

The excellent lubricating properties of the molecule may offer a conservative, safe and effective alternative to the existing treatments which offer less satisfactory results in application to certain joint dysfunctions (1,2, 4-7). The present study was therefore designed to determine whether the level of scientific evidence found in the literature justifies the recommendation of intraarticular HA injection in the clinical management of TMJD.

Material and Methods

A MEDLINE search was made covering the period between 1966 and 2008, applying synonyms and Medical Subject Headings (MeSH) first for temporomandibular joint dysfunction (TMJD) and then for hyaluronic acid (HA), with the purpose of generating a principal series of articles. Posteriorly, the identified literature was lim-

ited to human studies and articles published in English. Both search strategies were in turn combined by means of an "AND" boolean operator, thus crossing the articles on TMJD and HA.

Two of the authors analyzed the identified articles to determine whether they were pertinent to the study, with exclusion of those papers considered to be irrelevant. Then, separately and based on the SORT (Strength of Recommendation Taxonomy) criteria, the two authors stratified the studies according to their level of scientific evidence (9). This was followed by correlation of the results, and any observed discrepancies were subjected to discussion. If no consensus could be reached regarding the level of scientific evidence of a given article, another author was included in the discussion. Posteriorly, and according to the established level of evidence of the articles, a level of recommendation (in favor or against) was issued on the use of HA for the treatment of TMJD.

Results

The MEDLINE search yielded 10,000 articles for TMJD and 5956 for HA. As mentioned above, both search strategies were crossed to yield a pool of 28 articles. The article abstracts were then examined to establish whether the publications were relevant to the study subject. A total of 18 relevant articles were identified. These were critically reviewed and classified according to their level of scientific evidence. Posteriorly, and according to the results obtained by these articles, a level of recommendation (in favor or against) was established regarding the intraarticular injection of HA (9).

Table 1. The most relevant studies comparing different treatments (intraarticular injection), mainly between hyaluronic acid (HA), glucocorticoids (CO) and saline solution (SA).

Authors	Year	Level of evidence	Sample size	Injection	Dose-times	Results
Kopp et al.(10)	1991	1	14 14 13	HA CO SA	0.7 ml x 2 every 2 weeks	CO>HA
Kopp et al.(5)	1987	1	15 12	HA CO	0.5 ml x 2 every 2 weeks	HA>CO
Sato et al.(4, 14, 17)	2001 2001 1997	2	60 + 76 59 + 62 26 + 50	Anesthesia, drainage+HA Control	1 ml every week for 5 weeks	HA>control
Hepguler et al.(1)	2002	1	19 19	HA SA	0.5 ml every week, for 6 months	HA>SA
Alpaslan et al.(2)	2001	1	31	Anesthesia, SA ± HA	200-300 ml ± 1 ml, a single time	Arthrocentesis with HA>without HA
McCain et al.(11)	1989	1	33 22	Hylan fluid Control	3 ml + abundant SA	Hylan fluid ≥HA
Møystad et al.(13)	2008	1	20 20	HA CO	2 injections 2 weeks apart	HA = CO
Bjørnland et al.(12)	2007	1	20 20	Anesthesia and HA Anesthesia and CO	2 injections of 0.7-1 ml 14 days apart	HA > CO

The analysis yielded 9 articles with level of evidence 1 (1-3, 5,8, 10-13), and 7 with level of evidence 2 (4,6,7, 14-17). The 9 publications classified as being of high quality were randomized double-blind studies with adequate sample sizes, parallel groups, statistical analysis and adequate follow-up. On the other hand, the 7 publications classified as presenting limited quality evidence were non-randomized studies with an adequate sample size, parallel groups, statistical analysis and adequate follow-up. Based on these publications we established strength of recommendation A in favor of the use of HA in the treatment TMJD: reducible disc displacement (RDD), non-reducible disc displacement (NRDD), and other degenerative joint diseases.

The characteristics of the reviewed studies allowed us to include them in groups according to the treatments prescribed. Three types of comparisons were identified: HA versus placebo, HA versus glucocorticoids (CO), and arthroscopy or arthrocentesis combined with HA versus arthroscopy or arthrocentesis with placebo (Table 1).

Discussion

Hyaluronic acid (HA) is the principal natural component of synovial fluid. Although it has great importance in joint lubrication, the mechanism by which HA affords improvement in joint disease is not entirely clear. In the relevant studies found in the literature, HA was compared with placebo, glucocorticoids (CO) and combined with other surgical treatments (arthroscopy or arthrocentesis). The Helkimo clinical dysfunction index and subjective symptoms of mandibular function, pain and joint sounds as measured by multiple response questionnaires and a visual analog scale (VAS) provided an indication as to the positive or negative recommendation of treatment with HA.

Comparing hyaluronic acid with placebo, Bertolami et al. (3) designed a multicenter study with a duration of 6 months in which they examined the effects of the intraarticular injection of HA in 80 patients (experimental group): 35 with reducible disc displacement (RDD), 8 with non-reducible disc displacement (NRDD), and 37 with degenerative joint disease (DJD). The placebo group included 41 patients: 15 with RDD, 6 with NRDD and 20 with DJD. For measuring joint dysfunction and the course after treatment, the authors used two indexes proposed by Helkimo: the anamnesis index for describing patient perception of the clinical problem and treatment efficacy, and the clinical dysfunction index for determining the functional condition of the joint. The results showed significant improvement of these indexes in the RDD patients treated with HA versus the placebo group. In patients with NRDD and DJD, improvement was seen in both groups, though without statistically significant differences between them.

Patients with very advanced-stage DJD or with ankylosis of the TMJ generally caused by trauma may require surgery to solve the problem (18).

Hepgulger et al. (1) examined the efficacy of HA in 38 patients with RDD. These authors used a VAS to assess pain and the intensity of joint sounds, together with a modification of the Helkimo clinical dysfunction index. The evaluation was made before the first application, after one month and again after 6 months. The authors recorded significant improvement of all the symptoms in 17 (89.5%) of the 19 RDD patients treated with HA, while the placebo group showed no significant variations - with the exception of pain, which improved after one and 6 months. In these two well designed, randomized and double blind high-quality studies, HA was applied to a total of 54 patients with RDD, with clinical improvement in relation to joint sounds and mandibular deviation, as well as partial remission of the symptoms assessed by the Helkimo index. The results of these authors (1, 3) present strength of recommendation type A favorable to the intraarticular application of HA in patients with RDD.

In relation to NRDD, Sato et al. (4,7,14,17) examined maximum oral opening, laterality, TMJ pain and masticatory muscle discomfort in patients with this type of disc displacement. The authors showed the intraarticular injection of HA to be significantly more effective in securing clinical symptoms remission after 6, 12 and 24 months than simple conservative observation of NRDD. Using electromyography (EMG) and mandibular kinesiography (MKG), Sato et al. (15,16) in 20 patients with NRDD likewise found the intraarticular injection of HA to allow near normalization of the duration of contraction, masseter and temporal muscle function, and chewing movements and efficacy. It can be seen that although the injection of HA does not improve disc position or deformation, the symptoms subside and oral opening can increase even in those cases where disc deformation and displacement persist. Of these publications by Sato et al. (15,16), we highlight the observation that the intraarticular application of HA improves function and reduces pain in patients with NRDD. The different studies carried out by Sato et al. involve a correct clinical follow-up period of between 6 and 24 months, and have an adequate sample size. Nevertheless, their quality is limited, since they are not randomized. As a result, in NRDD, the strength of recommendation for the application of HA, while still positive, is of type B in these studies (4,7, 14-17).

The patients with rheumatoid arthritis studied by Kopp et al. (10) obtained improvement of the symptoms such as TMJ pain and pain in different facial zones, difficulty in opening the mouth, joint sounds and pain in other joints, as measured by a multiple response questionnaire, a visual analog scale (VAS) and the Helkimo

clinical dysfunction index. The end symptoms, compared with the situation before treatment, had improved in 10 of the 14 patients treated with HA, and in 9 of the 13 patients of the placebo group. The mean symptoms reduction on the VAS was 11 mm in the HA group and 8 mm in the placebo group, while the clinical dysfunction index showed a mean 5-point reduction in both groups. This is the only high quality study in which HA is compared with placebo in patients with rheumatoid arthritis (10). The results yielded type A recommendation that is neither in favor nor against the intraarticular injection of HA in the treatment of this type of temporomandibular disorder.

Comparison has also been made of the effect of HA versus glucocorticoids (CO). Kopp et al. (10) used the intraarticular injection of HA or CO in patients with TMJD refractory to conservative management. The symptoms were evaluated by the clinical dysfunction index, and by a 10-item questionnaire including the assessment of TMJ pain and pain in different zones of the face, difficulty opening the mouth, joint sounds, the duration of symptoms, and pain in other joints. The authors recorded improvement in both groups, with symptoms remission in 13 of the 18 patients treated with HA and in 9 of the 15 patients treated with CO after four weeks of follow-up. In another similar study by the same authors (5) and involving two years of follow-up, similar improvement was recorded for both types of treatment (HA and CO) according to the clinical dysfunction index. Nevertheless, Bjørnland et al. (12) considered that HA injections are more effective than CO in combating the intensity of pain, and that patients only presenting TMJ pain (without added myofascial pain) are the best candidates for this type of treatment. Regardless of whether HA or CO is injected, we at least can be sure that there will be no bone structural changes, as evidenced by Møystad et al. (13), in their study of 36 patients with osteoarthritis in both TMJs.

Two studies (5,10) evaluated a total of 74 patients with TMJD assigned randomly and on a blind basis to either HA (32 cases) or CO (29 cases). The results showed HA efficacy in securing remission of the symptoms of TMJD to be similar to that recorded in the CO group with no statistically significant differences between the two treatments in terms of oral opening and muscle or joint pain. Given the high quality of these studies, type A recommendation can be assumed, and the positive effects of both treatments over the short and long term are favorable to both the intraarticular application of HA and the use of CO in the treatment of TMJD.

The combination of HA with surgical procedures (arthroscopy or arthrocentesis) versus placebo with the same procedures has been examined by McCain et al. (11). The authors carried out a total of 55 arthroscopic procedures in the TMJ: 33 with HA injection and 22

controls that received the injection of Ringer lactate solution. The authors assessed the efficacy of the instruments, visualization and arthroscopic imaging quality, the control of detritus, the control of intracapsular bleeding and tissue debridement. They found that the intraarticular application of HA during arthroscopy significantly improved these parameters in comparison with the controls. They likewise observed no short- or long-term complications of the use of HA.

The efficacy of arthrocentesis (AC) with and without the injection of HA was analyzed by Alpaslan et al. (2) in 41 joints of 31 patients with TMJD, 19 TMJs with RDD and 22 with joint block. The evaluation of the patients was made before the procedure, immediately afterwards, and postoperatively up until 24 months. The parameters recorded were maximum oral opening, laterality, pain intensity, mandibular function and the presence of sounds as assessed by a VAS. The authors observed increased oral opening, laterality and mandibular function that barely proved significant for the patients treated with AC and HA. Nevertheless, the pain and sounds decreased in both groups. The reduction in pain was greater in the AC and HA group.

In another study, Alpaslan et al. (6) evaluated the nitrite, nitrate and thiobarbituric acid levels in 25 patients with TMJD: 10 treated with AC and 15 with AC and HA. The authors recorded significant improvement in mandibular function and a likewise significant reduction in nitrite, nitrate and thiobarbituric acid levels in the patients treated with AC and HA.

From the analysis of the study published by McCain et al. (11), positive type A recommendation was deduced for the combined application of arthroscopy with HA, in view of the benefits afforded by viscosurgery during this surgical procedure in protecting the joint surfaces and facilitating the operation. However, as regards its effects upon the clinical symptoms, the authors found that the combination did not offer significant improvements. On the other hand, the studies of Alpaslan et al. (2,6) yielded type A recommendation (2) and type B recommendation (6) favorable to the combination of arthrocentesis with HA—both studies showing this combination to significantly improve the clinical signs and symptoms of patients with TMJD.

The Cochrane review suggests that HA can offer long-term improvement of the signs and symptoms of TMJD, that its beneficial effects are on a par with those offered by glucocorticoids, and that some of the benefits can be obtained on combining with other techniques such as arthrocentesis or arthroscopy (8).

Based on the evidence found in the literature, we consider that a multicenter, randomized, placebo-controlled double-blind study with a sufficiently large patient sample, well defined TMJD groups and the use of objective variables is absolutely necessary in order to establish

the true therapeutic effects of the intraarticular injection of HA in patients with TMJD, and to define the best posology.

References

- Hepguler S, Akkoc YS, Pehlivan M, Ozturk C, Celebi G, Saracoglu A, et al. The efficacy of intra-articular sodium hyaluronate in patients with reducing displaced disc of the temporomandibular joint. *J Oral Rehabil.* 2002;29:80-6.
- Alpaslan GH, Alpaslan C. Efficacy of temporomandibular joint arthrocentesis with and without injection of sodium hyaluronate in treatment of internal derangements. *J Oral Maxillofac Surg.* 2001;59:613-8.
- Bertolami CN, Gay T, Clark GT, Rendell J, Shetty V, Liu C, et al. Use of sodium hyaluronate in treating temporomandibular joint disorders: a randomized, double-blind, placebo-controlled clinical trial. *J Oral Maxillofac Surg.* 1993;51:232-42.
- Sato S, Oguri S, Yamaguchi K, Kawamura H, Motegi K. Pumping injection of sodium hyaluronate for patients with non-reducing disc displacement of the temporomandibular joint: two year follow-up. *J Craniomaxillofac Surg.* 2001;29:89-93.
- Kopp S, Carlsson GE, Haraldson T, Wenneberg B. Long-term effect of intra-articular injections of sodium hyaluronate and corticosteroid on temporomandibular joint arthritis. *J Oral Maxillofac Surg.* 1987;45:929-35.
- Alpaslan C, Bilgihan A, Alpaslan GH, Güner B, Özgür Yis M, Erbaş D. Effect of arthrocentesis and sodium hyaluronate injection on nitrite, nitrate, and thiobarbituric acid-reactive substance levels in the synovial fluid. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000;89:686-90.
- Sato S, Sakamoto M, Kawamura H, Motegi K. Disc position and morphology in patients with nonreducing disc displacement treated by injection of sodium hyaluronate. *Int J Oral Maxillofac Surg.* 1999;28:253-7.
- Shi Z, Guo C, Awad M. Hyaluronate for temporomandibular joint disorders. *Cochrane Database Syst Rev.* 2003;1:CD002970.
- Ebell MH, Siwek J, Weiss BD, Woolf SH, Susman J, Ewigman B, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician.* 2004;69:548-56.
- Kopp S, Akerman S, Nilner M. Short-term effects of intra-articular sodium hyaluronate, glucocorticoid, and saline injections on rheumatoid arthritis of the temporomandibular joint. *J Craniomandib Disord.* 1991;5:231-8.
- McCain JP, Balazs EA, de la Rúa H. Preliminary studies on the use of a viscoelastic solution in arthroscopic surgery of the temporomandibular joint. *J Oral Maxillofac Surg.* 1989;47:1161-8.
- Bjørnland T, Gjaerum AA, Møystad A. Osteoarthritis of the temporomandibular joint: an evaluation of the effects and complications of corticosteroid injection compared with injection with sodium hyaluronate. *J Oral Rehabil.* 2007;34:583-9.
- Møystad A, Mork-Knutsen BB, Bjørnland T. Injection of sodium hyaluronate compared to a corticosteroid in the treatment of patients with temporomandibular joint osteoarthritis: a CT evaluation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2008;105:e53-60.
- Sato S, Goto S, Kasahara T, Kawamura H, Motegi K. Effect of pumping with injection of sodium hyaluronate and the other factors related to outcome in patients with non-reducing disk displacement of the temporomandibular joint. *Int J Oral Maxillofac Surg.* 2001;30:194-8.
- Sato S, Nasu F, Motegi K. Analysis of post-treatment electromyographs in patients with non-reducing disc displacement of the temporomandibular joint. *J Oral Rehabil.* 2002;29:1126-30.
- Sato S, Nasu F, Motegi K. Analysis of kinesiograph recordings and masticatory efficiency after treatment of non-reducing disk displacement of the temporomandibular joint. *J Oral Rehabil.* 2003;30:708-13.
- Sato S, Ohta M, Ohki H, Kawamura H, Motegi K. Effect of lavage with injection of sodium hyaluronate for patients with nonreducing disk displacement of the temporomandibular joint. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1997;84:241-4.
- Vasconcelos BC, Bessa-Nogueira RV, Cypriano RV. Treatment of temporomandibular joint ankylosis by gap arthroplasty. *Med Oral Patol Oral Cir Bucal.* 2006;11:E66-9.

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